

FILE 'AGRICOLA, ALUMINIUM, ANABSTR, BABS, BIOCOMMERCE, BIOTECHNO, CABA,
CAOLD, CAPLUS, CBNB, CEABA-VTB, CEN, CERAB, CIN, COMPENDEX, CONFSCI,
COPPERLIT, CORROSION, DKILIT, ENCOMPLIT, ENCOMPLIT2, FEDRIP, GENBANK,
INSPEC, INSPHYS, INVESTEXT, IPA, JICST-EPLUS, ...' ENTERED AT 16:32:56 ON
31 AUG 2002

L1 37 S PHOSPHONATE PRODRUG
L2 2 S L1 AND ETOPOSIDE

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L2 ANSWER 1 OF 2 USPATFULL
AN 2002:99444 USPATFULL
TI Novel prodrugs for phosphorus-containing compounds
IN Erion, Mark D., Del Mar, CA, UNITED STATES
Reddy, K. Raja, San Diego, CA, UNITED STATES
Robinson, Edward D., San Diego, CA, UNITED STATES
Ugarkar, Bheemarao G., San Diego, CA, UNITED STATES
PI US 2002052345 A1 20020502
AI US 2001-978454 A1 20011015 (9)
RLI Continuation of Ser. No. US 1999-392352, filed on 8 Sep 1999, GRANTED,
Pat. No. US 6312662 Continuation-in-part of Ser. No. US 1999-263976,
filed on 5 Mar 1999, PENDING
PRAI US 1998-77164P 19980306 (60)
US 1998-77165P 19980306 (60)
DT Utility
FS APPLICATION
LN.CNT 8663
INCL INCLM: 514/079.000
INCLS: 514/110.000
NCL NCLM: 514/079.000
NCLS: 514/110.000
IC [7]
ICM: A61K031-675
ICS: A61K031-66
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L2 ANSWER 2 OF 2 USPATFULL
AN 2001:196573 USPATFULL
TI Prodrugs phosphorus-containing compounds
IN Erion, Mark D., Del Mar, CA, United States
Reddy, K. Raja, San Diego, CA, United States
Robinson, Edward D., San Diego, CA, United States
Ugarkar, Bheemarao G., San Diego, CA, United States
PA Metabasis Therapeutics, Inc., San Diego, CA, United States (U.S.
corporation)
PI US 6312662 B1 20011106
AI US 1999-392352 19990908 (9)
RLI Continuation-in-part of Ser. No. US 1999-263976, filed on 5 Mar 1999
PRAI US 1998-77164P 19980306 (60)
DT Utility
FS GRANTED
LN.CNT 9069
INCL INCLM: 424/009.100
INCLS: 424/600.000; 424/001.110; 424/009.200; 424/001.650; 424/601.000;
514/007.000
NCL NCLM: 424/009.100
NCLS: 424/001.110; 424/001.650; 424/009.200; 424/600.000; 424/601.000;
514/007.000
IC [7]
ICM: A61K049-00
EXF 424/1.11; 424/1.65; 424/1.77; 424/9.1; 424/9.2; 424/600; 424/601;
424/603; 514/7
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L3 ANSWER 1 OF 4 USPATFULL
 AN 97:46134 USPATFULL
 TI **Epipodophyllotoxin glucoside 4'-phosphate derivatives**
 IN Saulnier, Mark G., Middletown, CT, United States
 Senter, Peter D., Northeast Seattle, WA, United States
 Kadow, John F., Wallingford, CT, United States
 PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)
 PI US 35524 19970603
 US 4904768 19900227 (Original)
 AI US 1994-229659 19940419 (8)
 US 1988-199731 19880527 (Original)
 RLI Continuation-in-part of Ser. No. US 1987-81492, filed on 4 Aug 1987, now abandoned
 DT Reissue
 FS Granted
 LN.CNT 871
 INCL INCLM: 536/017.100
 INCLS: 536/004.100; 536/017.200; 536/018.100; 536/018.200; 536/018.500; 536/117.000; 536/124.000
 NCL NCLM: 536/017.100
 NCLS: 536/004.100; 536/017.200; 536/018.100; 536/018.200; 536/018.500; 536/117.000; 536/124.000
 IC [6]
 ICM: C07H011-04
 ICS: C07H015-00
 EXF 536/4.1; 536/18.1; 536/17.2; 536/18.2; 536/18.5; 536/17.1; 536/117; 536/124; 514/33; 514/34; 514/35; 514/908
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 TI **Epipodophyllotoxin glucoside 4'-phosphate derivatives**
 SUMM The present invention relates to 4'-phosphate derivatives of **epipodophyllotoxin** glucosides, to their antitumor use, and to pharmaceutical compositions containing these new agents.
 SUMM . . . Keller-Juslen et al. The compounds disclosed therein, in particular etoposide and teniposide, serve as starting material for our preparation of **epipodophyllotoxin glucoside 4'-phosphate derivatives** of the present invention. ##STR1##
 SUMM The present invention provides **phosphate esters** of 4'-demethylepipodophyllotoxin glucosides which are active antitumor agents. In particular, the dihydrogen phosphate of 4'-demethylepipodophyllotoxin glucosides and salts thereof are. . .
 SUMM . . . to favor one or the other reaction product. For example, when a large excess of the amine relative to the **epipodophyllotoxin** is used, the symmetrical phosphorodiamidate is obtained, i.e. compounds of formula VII wherein Y is the same as NR.sup.2 R.sup.3. . .
 SUMM . . . compounds of formula V wherein R.sup.7 and R.sup.8 are not H, and they may be prepared by treating a 4'-demethylepipodophyllotoxin **glucoside** with a halophosphate diester, [i.e. Hal-P(X) (OR.sup.7) (OR.sup.8)]. It has been found that this reaction is most efficiently performed in acetonitrile. . . base is used, but both reagents are preferably employed in molar equivalents in slight excess relative to that of the **epipodophyllotoxin glucoside** reactant.
 The reaction may be carried out at any temperature conducive to product formation; however, slightly elevated temperatures, e.g. 30.degree.-40.degree.. . .
 L3 ANSWER 2 OF 4 USPATFULL
 AN 91:66777 USPATFULL
 TI **Epipodophyllotoxin glucoside 4'-phosphate**

derivatives

IN Saulnier, Mark G., Middletown, CT, United States
 Senter, Peter D., Seattle, WA, United States
 Kadow, John F., Meriden, CT, United States

PA Bristol-Myers Company, New York, NY, United States (U.S. corporation)

PI US 5041424 19910820

AI US 1989-450718 19891214 (7)

RLI Division of Ser. No. US 1988-199731, filed on 27 May 1988, now patented,
 Pat. No. US 4904768 which is a continuation-in-part of Ser. No. US
 1987-81493, filed on 4 Aug 1987, now abandoned

DT Utility

FS Granted

LN.CNT 704

INCL INCLM: 514/027.000
 INCLS: 514/033.000; 536/017.100; 536/018.100

NCL NCLM: 514/027.000
 NCLS: 514/033.000; 536/017.100; 536/018.100

IC [5]
 ICM: A61K031-70
 ICS: C07H015-24

EXF 536/17.1; 536/18.1; 514/27; 514/33; 514/35

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Epipodophyllotoxin glucoside 4'-phosphate**
 derivatives

SUMM The present invention relates to 4'-phosphate derivatives of
epipodophyllotoxin glucosides, to their antitumor use, and to
 pharmaceutical compositions containing these new agents.

SUMM . . . Keller-Juslen et al. The compounds disclosed therein, in
 particular etoposide and teniposide, serve as starting material for our
 preparation of **epipodophyllotoxin glucoside**
 4'-phosphate derivatives of the present invention. ##STR1##

SUMM The present invention provides **phosphate esters** of
 4'-demethylepipodophyllotoxin glucosides which are active antitumor
 agents. In particular, the dihydrogen phosphate of 4'-
 demethylepipodophyllotoxin glucosides and salts thereof are. . .

SUMM . . . to favor one or the other reaction product. For example, when a
 large excess of the amine relative to the **epipodophyllotoxin**
 is used, the symmetrical phosphorodiamidate is obtained, i.e. compounds
 of formula VII wherein Y is the same as NR.sup.2 R.sup.3. . .

SUMM . . . compounds of formula V wherein R.sup.7 and R.sup.8 are not H,
 and they may be prepared by treating a 4'-demethylepipodophyllotoxin
glucoside with a halophosphate diester, [i.e.
 Hal-P(X) (OR.sup.7) (OR.sup.8)]. It has been found that this reaction is
 most efficiently performed in acetonitrile in. . . base is used, but
 both reagents are preferably employed in molar equivalents in slight
 excess relative to that of the **epipodophyllotoxin**
glucoside reactant. The reaction may be carried out at any
 temperature conducive to product formation; however, slightly elevated
 temperatures, e.g. 30.degree.-40.degree.. . .

L3 ANSWER 3 OF 4 USPATFULL

AN 90:28028 USPATFULL

TI Phosphorus containing derivatives of **epipodophyllotoxin**

IN Saulnier, Mark G., Middletown, CT, United States

PA Bristol-Myers Company, New York, NY, United States (U.S. corporation)

PI US 4916217 19900410

AI US 1987-1281 19870108 (7)

DT Utility

FS Granted

LN.CNT 501

INCL INCLM: 536/017.100
 INCLS: 536/004.100; 536/018.100; 536/117.000

L4 ANSWER 3 OF 4 USPATFULL

TI Phosphorus containing derivatives of **epipodophyllotoxin**

SUMM The present invention provides phosphorous containing derivatives of **epipodophyllotoxin glucoside** aldehyde or ketone condensation products which have the ability to inhibit transplanted tumors in experimental animals and to the therapeutic. . . .

SUMM . . . podophyllotoxin (III). The numbering system used for nomenclature purposes is shown in Formula III. Note that podophyllotoxin and etoposide, an **epipodophyllotoxin** derivative, are epimeric at the 4-position. Etoposide and teniposide are active in the treatment of a variety of cancers including. . . .

SUMM The present invention is concerned with **epipodophyllotoxin** derivatives of Formula V wherein R.sup.4 and R.sup.5 represent the carbonyl attached groups of an aldehyde or ketone of the formula R.sup.4 R.sup.5 CO which is capable of condensing with **epipodophyllotoxin glucoside** as described in the Keller-Juslen patent cited above, U.S. Pat. No. 3,524,844. R.sup.6 has one of Formulas Va, Vb, or. . . .

SUMM . . . are cyclic oxyphosphoranes of Formula Va. In the case of phosphite reactants of Formula VII, the products are mixtures of **phosphate esters** of Formulas Vb and Vc. Generally the phosphate ester mixtures may be used without separation for the antitumor purposes of. . . .

SUMM . . . the cyclic pentacovalent phosphate species of Formula V wherein R.sup.6 has Formula Vd enjoys an existence in solutions of the **esters** of Formulas Vb and Vc.

NCL NCLM: 536/017.100
NCLS: 536/004.100; 536/018.100; 536/117.000
IC [4]
ICM: C07H015-00
ICS: C07H017-00
EXF 536/18.1; 536/17.1; 536/1; 536/117; 536/4.1; 514/27; 514/34
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Phosphorus containing derivatives of **epipodophyllotoxin**
SUMM The present invention provides phosphorous containing derivatives of
epipodophyllotoxin glucoside aldehyde or ketone
condensation products which have the ability to inhibit transplanted
tumors in experimental animals and to the therapeutic. . .
SUMM . . . podophyllotoxin (III). The numbering system used for
nomenclature purposes is shown in Formula III. Note that podophyllotoxin
and etoposide, an **epipodophyllotoxin** derivative, are epimeric
at the 4-position. Etoposide and teniposide are active in the treatment
of a variety of cancers including. . .
SUMM The present invention is concerned with **epipodophyllotoxin**
derivatives of Formula V wherein R.sup.4 and R.sup.5 represent the
carbonyl attached groups of an aldehyde or ketone of the formula R.sup.4
R.sup.5 CO which is capable of condensing with
epipodophyllotoxin glucoside as described in the
Keller-Juslen patent cited above, U.S. Pat. No. 3,524,844. R.sup.6 has
one of Formulas Va, Vb, or. . .
SUMM . . . are cyclic oxyphosphoranes of Formula Va. In the case of
phosphite reactants of Formula VII, the products are mixtures of
phosphate esters of Formulas Vb and Vc. Generally the
phosphate ester mixtures may be used without separation for the
antitumor purposes of. . .
L3 ANSWER 4 OF 4 USPATFULL
AN 90:15656 USPATFULL
TI **Epipodophyllotoxin glucoside 4'-phosphate**
derivatives
IN Saulnier, Mark G., Middletown, CT, United States
Senter, Peter D., Seattle, WA, United States
Kadow, John F., Meriden, CT, United States
PA Bristol-Myers Company, New York, NY, United States (U.S. corporation)
PI US 4904768 19900227
AI US 1988-199731 19880527 (7)
RLI Continuation-in-part of Ser. No. US 1987-81493, filed on 4 Aug 1987, now
abandoned
DT Utility
FS Granted
LN.CNT 794
INCL INCLM: 536/017.100
INCLS: 536/004.100; 536/017.200; 536/018.100; 536/018.200; 536/018.500;
536/117.000; 514/908.000
NCL NCLM: 536/017.100
NCLS: 514/908.000; 536/004.100; 536/017.200; 536/018.100; 536/018.200;
536/018.500; 536/117.000
IC [4]
ICM: C07H011-04
ICS: C07H015-00
EXF 536/4.1; 536/18.1; 536/17.2; 536/18.2; 536/18.5; 536/117; 536/17.1;
514/33; 514/34; 514/35; 514/908
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI **Epipodophyllotoxin glucoside 4'-phosphate**
derivatives
SUMM The present invention relates to 4'-phosphate derivatives of
epipodophyllotoxin glucosides, to their antitumor use, and to
pharmaceutical compositions containing these new agents.

SUMM . . . Keller-Juslen et al. The compounds disclosed therein, in particular etoposide and teniposide, serve as starting material for our preparation of **epipodophyllotoxin glucoside** 4'-phosphate derivatives of the present invention. ##STR1##

SUMM The present invention provides **phosphate esters** of 4'-demethylepipodophyllotoxin glucosides which are active antitumor agents. In particular, the dihydrogen phosphate of 4'-demethylepipodophyllotoxin glucosides and salts thereof are. . .

DETD . . . to favor one or the other reaction product. For example, when a large excess of the amine relative to the **epipodophyllotoxin** is used, the symmetrical phosphorodiamidate is obtained, i.e. compounds of formula VII wherein Y is the same as NR.sup.2 R.sup.3. . .

DETD . . . compounds of formula V wherein R.sup.7 and R.sup.8 are not H, and they may be prepared by treating a 4'-demethylepipodophyllotoxin **glucoside** with a halophosphate diester, [i.e. Hal-P(X) (OR.sup.7) (OR.sup.8)]. It has been found that this reaction is most efficiently performed in acetonitrile in. . . base is used, but both reagents are preferably employed in molar equivalents in slight excess relative to that of the **epipodophyllotoxin glucoside** reactant. The reaction may be carried out at any temperature conducive to product formation; however, slightly elevated temperatures, e.g. 30.degree.-40.degree.. . .

=>

L2 ANSWER 1 OF 2 USPATFULL
 AN 2002:99444 USPATFULL
 TI Novel prodrugs for phosphorus-containing compounds
 IN Erion, Mark D., Del Mar, CA, UNITED STATES
 Reddy, K. Raja, San Diego, CA, UNITED STATES
 Robinson, Edward D., San Diego, CA, UNITED STATES
 Ugarkar, Bheemarao G., San Diego, CA, UNITED STATES
 PI US 2002052345 A1 20020502
 AI US 2001-978454 A1 20011015 (9)
 RLI Continuation of Ser. No. US 1999-392352, filed on 8 Sep 1999, GRANTED,
 Pat. No. US 6312662 Continuation-in-part of Ser. No. US 1999-263976,
 filed on 5 Mar 1999, PENDING
 PRAI US 1998-77164P 19980306 (60)
 US 1998-77165P 19980306 (60)
 DT Utility
 FS APPLICATION
 LN.CNT 8663
 INCL INCLM: 514/079.000
 INCLS: 514/110.000
 NCL NCLM: 514/079.000
 NCLS: 514/110.000
 IC [7]
 ICM: A61K031-675
 ICS: A61K031-66
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 DETD [0372] Oncolytic drugs such as **etoposide**, topotecan, taxol,
 etc. that contain a biologically important hydroxyl or oncolytic drugs
 such as mitomycin, anthracyclin antibiotics (e.g. dioxorubicin) that.
 DETD [0374] Oncolytic drugs such as **etoposide**, topotecan, taxol,
 etc. that contain a biologically important hydroxyl or oncolytic drugs
 such as mitomycin, methotrexate, anthracyclin antibiotics (e.g.
 dioxorubicin).
 DETD . . . Z are --H, W and V are both the same aryl, substituted aryl,
 heteroaryl, or substituted heteroaryl such that the **phosphonate**
prodrug moiety: ##STR25##
 DETD [0680] The **phosphonate prodrug** esters where spacer
 group X in formula II-IV is an aryl group, can be prepared by lithiation
 of aromatic ring.
 CLM What is claimed is:
 . . . Z are --H, W and V are both the same aryl, substituted aryl,
 heteroaryl, or substituted heteroaryl such that the **phosphonate**
prodrug moiety: ##STR83## has a plane of symmetry.

L2 ANSWER 2 OF 2 USPATFULL
 AN 2001:196573 USPATFULL
 TI Prodrugs phosphorus-containing compounds
 IN Erion, Mark D., Del Mar, CA, United States
 Reddy, K. Raja, San Diego, CA, United States
 Robinson, Edward D., San Diego, CA, United States
 Ugarkar, Bheemarao G., San Diego, CA, United States
 PA Metabasis Therapeutics, Inc., San Diego, CA, United States (U.S.
 corporation)
 PI US 6312662 B1 20011106
 AI US 1999-392352 19990908 (9)
 RLI Continuation-in-part of Ser. No. US 1999-263976, filed on 5 Mar 1999
 PRAI US 1998-77164P 19980306 (60)
 DT Utility
 FS GRANTED
 LN.CNT 9069

INCL INCLM: 424/009.100
INCLS: 424/600.000; 424/001.110; 424/009.200; 424/001.650; 424/601.000;
514/007.000
NCL NCLM: 424/009.100
NCLS: 424/001.110; 424/001.650; 424/009.200; 424/600.000; 424/601.000;
514/007.000

IC [7]
ICM: A61K049-00

EXF 424/1.11; 424/1.65; 424/1.77; 424/9.1; 424/9.2; 424/600; 424/601;
424/603; 514/7

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Oncolytic drugs such as **etoposide**, topotecan, taxol, etc. that
contain a biologically important hydroxyl or oncolytic drugs such as
mitomycin, anthracyclin antibiotics (e.g. dioxorubicin) that. . .

DETD Oncolytic drugs such as **etoposide**, topotecan, taxol, etc. that
contain a biologically important hydroxyl or oncolytic drugs such as
mitomycin, methotrexate, anthracyclin antibiotics (e.g. dioxorubicin).

DETD . . . Z are --H, W and V are both the same aryl, substituted aryl,
heteroaryl, or substituted heteroaryl such that the **phosphonate**
prodrug moiety: ##STR25##

DETD The **phosphonate prodrug** esters where spacer group X
in formula II-IV is an aryl group, can be prepared by lithiation of
aromatic ring. . .

CLM What is claimed is:

. . . Z are --H, W and V are both the same aryl, substituted aryl,
heteroaryl, or substituted heteroaryl such that the **phosphonate**
prodrug moiety: ##STR84## has a plane of symmetry.

FILE 'AGRICOLA, ALUMINIUM, ANABSTR, BABS, BIOCOMMERCE, BIOTECHNO, CABA,
CAOLD, CAPLUS, CBNB, CEABA-VTB, CEN, CERAB, CIN, COMPENDEX, CONFSCI,
COPPERLIT, CORROSION, DKILIT, ENCOMPLIT, ENCOMPLIT2, FEDRIP, GENBANK,
INSPEC, INSPHYS, INVESTEXT, IPA, JICST-EPLUS, ...' ENTERED AT 16:32:56 ON
31 AUG 2002

L1 37 S PHOSPHONATE PRODRUG
L2 2 S L1 AND ETOPOSIDE